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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/821,850	03/29/2001	Michael P. Bevilacqua	2331/112US	3553

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EXAMINER
ALLEN, MARIANNE P

ART UNIT	PAPER NUMBER
1631	16

DATE MAILED: 12/24/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/821,850	BEVILACQUA ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,43-155 and 167-179* is/are pending in the application.

4a) Of the above claim(s) *1-35 and 43-155* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *167-179* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-35,43-155 and 167-179* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7, 12* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of claims 167-174 in Paper No. 14 is acknowledged. Claims 175-179 directed to the same invention were also added in this response.

Claims 1-35 and 43-155 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14.

Information Disclosure Statement

It appears from the designation of "supplemental" information disclosure statements submitted on 5/29/01 and 7/1/02 that another IDS was submitted prior to these dates. However, no additional IDS is present in the application. If a prior IDS was submitted, applicant is requested to resubmit it with proof that it was received in the Office.

Specification

The substitute specification filed 9/23/02 has been entered. However, it is noted that the description of the figures are now inconsistent with the figures as the specification has replaced the term "precision panel" with "selected panel" and the figure titles still use the term "precision panel." See at least Figures 23-24, 25C, and 26-36. It appears that applicant will need to correct the figures.

Claim Rejections - 35 USC § 112

Claims 167-179 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 167-174 are not originally filed claims and were added in the amendment filed 5/16/02. Basis is stated to be "throughout the specification" with particular reference to the preamble and element (b) of claim 1. The cancelled claims and various pages of the specification are also referenced. Claims 175-179 are not originally filed claims and were added in the amendment filed 9/23/02. Basis is stated to be the same as that for claims 167-174. However, the examiner is unable to find basis for these claims in any of the sections pointed to. In particular, claim 1 and cancelled claims 36-42 require production of a calibrated profile data set. Note that the reproducibility limitations are with respect to this calibrated profile data set. The specification does not appear to disclose nor contemplate a method with these limitations in the absence of a calibrated profile data set. (See at least claims 167 and 175 which do not recite a calibrated profile data set.) The specification does not appear to disclose nor contemplate a method with the recited efficiencies of amplification in the absence of a calibrated profile data set. In particular, the limitation of "specificity" being substantially similar for all constituents is not seen. (See claim 167.) In particular, the limitation of "substantially repeatable" is not seen. This language does not appear to be present in the originally filed claims and is not synonymous with the disclosure of "reproducible" on page 23. (See claims 167 and 175.) In particular, claims 169-171 use the language "lie within a range of approximately X percent." This language does not appear to be present in the originally filed claims and is not synonymous with the language in the specification at for example page 26 which recites, "differ by no more than approximately 10 %" and "differ by less than 1%."

The basis for "at least three" in claims 172 and 177 is stated to be on page 22 and claim 53. However, these disclosures are directed to from 3-100 genes which does not provide support for the broader concept now claimed. Likewise, the basis for "fewer than approximately 500" claims 173 and 178 is stated to be on page 23. However, this disclosure is directed to 100-500 genes which does not provide support for the broader concept now claimed.

The basis for the "coefficient of variation...less than approximately 3 percent" in claims 168 and 176 is stated to be on page 23. However, the disclosure of this coefficient of variation is in the context of a quadruplicate assay protocol which does not provide support for the broader concept now claimed.

The basis for the limitations of claims 174 and 179 is stated to be on page 22 and claims 31 and 32. However, these disclosures are in the context of the sample being different from the tissue or fluid where the condition is clinically manifested (claim 31) and the biological condition being a disease and the sample being different from the tissue or fluid that is the primary target (claim 32). These disclosures do not provide support for the broader concept now claimed. Note that the biological conditions being evaluated in the claims are not limited to clinical or disease conditions.

Should this new matter rejection be overcome, the claims would be subject to the enablement rejection as set forth below.

Claims 167-179 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the

art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

The preambles of claims 167 and 175 are directed to a method for evaluating a biological condition of a subject. However, the only positive and active step in claims 167 and 175 is to derive a profile data set from a sample. The claim does not have a step that results in evaluating a biological condition of a subject. As such, the methods are not enabled because the steps as written would not provide the required result of the preamble.

For those members of the profile dataset that are proteins, the specification does not disclose amplification of proteins or efficiencies of amplification therefore. Likewise, no specificities (of amplification?) are disclosed with respect to proteins. It appears that these limitations are only applicable to quantitative measures of RNA. The specification does not disclose nor provide guidance to measuring protein levels in these ways.

It appears that the crux of applicant's invention is optimizing amplification efficiency for measuring RNA amounts for the panel as a whole (paragraph bridging pages 23-24). Note that the specification defines "substantially similar" on page 26 as differing by no more than approximately 10%. This optimization is performed by using a consistent primer/template ratio and requiring a particular amplification efficiency (see page 26, first full paragraph). The specification indicates the primer-probe sets are designed and tested to determine those that meet the named parameters. The specification provides no guidance as to how the primer-probe sets are designed to give the desired result. Further, the specification implies that computer techniques known in the art for design are not sufficient and that experimental validation is required. While applicant provides specific panels in Tables 1-7, these tables give only the

names of the genes of interest. They do not provide the particular sequences of interest nor does the specification provide the primer-probe sets specific for any or all of these genes that result in the claimed specificity and efficiencies of amplification. It is noted that one of ordinary skill in the art would be unable to reproduce any of the experiments presented in the figures as insufficient information is provided in the specification to do so. No conditions are provided where the panel is composed of both proteins and RNA constituents. None of the examples appears to provide evidence demonstrating that the limitations of claims 168-171 and 176 were achieved for any panel or sample. It is noted for example, that Erlander et al. (WO 00/28092) at page 4 shows coefficients of variation on the order of 15% or greater. The examiner found no references that discussed determining a coefficient of variation any lower or in the range of the claimed limitation of 3%.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation." These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

The specification acknowledges that a large amount of experimentation would be required to develop the conditions that are substantially repeatable and where the specificity and efficiencies of amplification substantially similar.

Little direction or guidance is presented as to determining the primer-probe sets that would result in the claimed limitations for RNA measurements and none is provided for proteins.

The examples provide data but no underlying information as to what was done and how it was done such that the work could be reproduced and provide guidance to one practicing the invention. Many of the examples concern evaluating drug or agent effects that are not present in the instant methods and thus these examples are not directly applicable to the claimed invention. None of the examples appears to provide evidence demonstrating the limitations of claims 168-171 and 176 were achieved for any panel or sample.

With respect to the prior art, the specification asserts that the prior art has not optimized conditions for a panel as a whole. Thus, the specification should provide more guidance and direction to those of ordinary skill in the art as to how to implement or practice the invention.

While the skill of those in the art is high, the specification implies that it is not predictable which primer-probe sets would be suitable for the claimed method.

The claims broadly encompass evaluation of any biological condition by quantitating any distinct RNA or protein panel under conditions of substantial repeatability and amplification.

In order to practice the claimed methods, the skilled practitioner would first turn to the instant specification for guidance. However, the instant specification does not provide sufficient guidance to practice the claimed methods. As such, the skilled practitioner would turn to the prior art for such guidance, however the prior art does not provide such guidance. Finally, said practitioner would turn to trial and error experimentation to practice the full scope of the claimed invention without guidance from the specification or the prior art as to which embodiments of the claimed invention are operable. For all of these reasons, it is considered to require undue experimentation to practice the method of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 167, 169-173, 175, 177-178 are rejected under 35 U.S.C. 102(a) as being anticipated by Rodriguez-Antona et al. (Archives of Biochemistry and Biophysics, 376(1):109-166, 2000).

Applicant is being given benefit of only the instant filing date, namely 3/21/01. The invention as claimed is not disclosed in any of the parent or provisional applications relied upon for priority for at least the same reasons set forth in the new matter rejection above.

Rodriguez-Antona et al. discloses a quantitative RT-PCR assay to measure the mRNA content of ten known human CYP genes (the distinct RNA constituents) from human liver and cultured hepatocytes. These cytochrome P-450 enzymes are known to play a role in biotransformation of xenobiotics and thus quantitation of these genes can be considered as evaluating a biological condition. The assay amplifies the sequences simultaneously. The primers used were designed so that specificity and efficiency of amplification were similar. Reproducibility of the assay was demonstrated. See abstract, Tables I and III, Figure 3, pages 110-111, and pages 114-115. With respect to claim 169-171, Table I shows that each of the genes was amplified within a range of approximately 10 percent and at least four of the genes within a range of approximately 1 percent. With respect to claims 168 and 176, Figure 5 (closed bars) and page 112, right column, first full paragraph, demonstrate repeated testing of a sample

showing little intrassay variability; however, the standard deviation divided by the average * 100 (average coefficient of variation as set forth in the specification) does not appear to be less than approximately 3%.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 703-308-0666. The examiner can normally be reached on Monday-Friday, 8:30 am - 2:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward can be reached on 703-308-4028. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Marianne P. Allen
Primary Examiner
Art Unit 1631

mpa
December 19, 2002